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Stereodivergent Routes from Tyrosine to the 7-(*R*) and 7-(*S*) Diastereomers of the 7-Hydroxy-2,3,7,7a-Tetrahydroindole Ring Found in Gliotoxin

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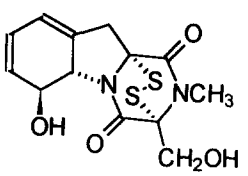
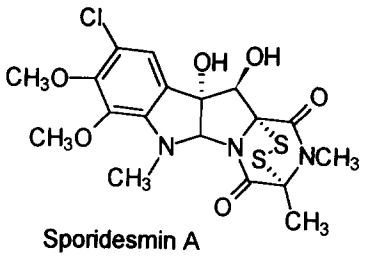
Abstract: Two routes from the oxidative cyclization product **1** derived from tyrosine to methyl 7-(*tert*-butyldimethylsiloxy)-*N*-(benzyloxycarbonyl)-2,3,7,7a-tetrahydroindole-2-carboxylate are described. The routes are stereodivergent leading to the 2-*S*,7-*S*,7a-*S* (**6**) and 2-*S*,7-*R*,7a-*S*-(**13**) diasteromers. The former stereochemistry corresponds to that present in gliotoxin.

The epidithioketopiperazine (EDTKP) fungal metabolites were originally isolated as the result of their toxicity.[1] Among this group of compounds the most studied are gliotoxin[2] and the sporidesmins.[3] More recently, interest in gliotoxin has resulted from its immunosuppressant activity.[4] Gliotoxin has also been observed to inhibit farnesylation of the Ras p21 protein[5a] and to induce apoptosis in thymocytes.[5b] Gliotoxin was synthesized in both racemic and enantiomerically pure form in the 1970's by Kishi and co-workers.[6] Their synthetic approach was to construct the dithioketopiperazine core in protected form and then close the dihydroindole ring. The enantioselective synthesis was based on resolution of an early intermediate. A similar strategy was used for sporidesmin A.[7] Since gliotoxin and the sporidesmins are biosynthetically derived from tyrosine and tryptophan, respectively, we were interested in exploring stereospecific synthetic pathways from the chiral aminoacids to the EDTKPs. In this paper we report two synthetic routes from tyrosine to the 7-hydroxy-2,3,7,7a-tetrahydro-1*H*-indole ring system found in gliotoxin. The two routes are stereodivergent leading to both the natural 7-(*S*) structure and the 7-(*R*) diastereoisomer.



Gliotoxin

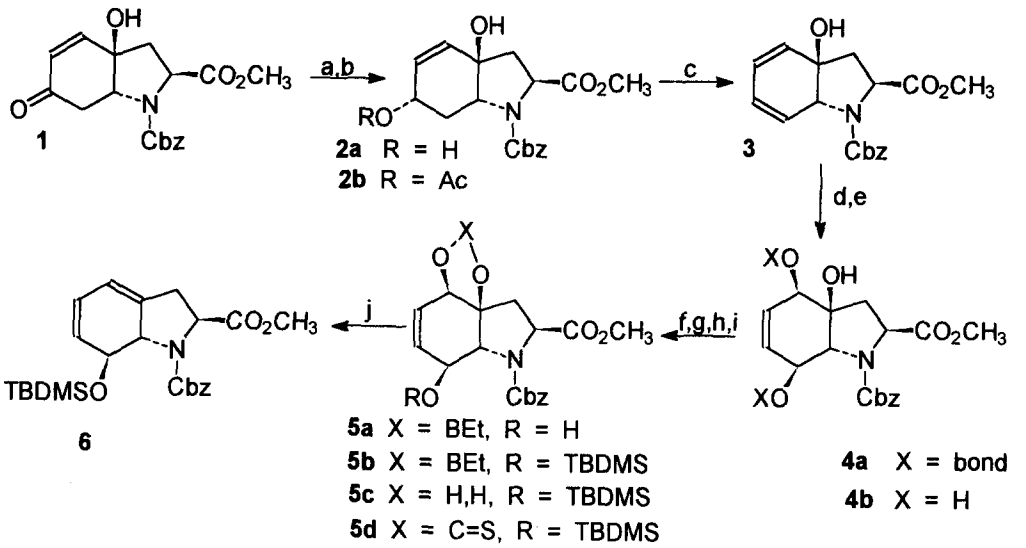


Sporidesmin A

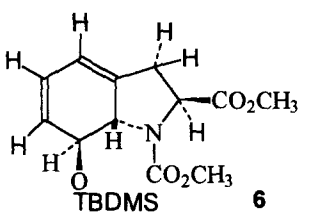
Results and Discussion

The gliotoxin molecule poses two major challenges for a synthetic route from tyrosine. The first, which is the topic of this paper, is the construction of the 7-hydroxytetrahydroindole ring with correct stereochemistry. The second is construction of the epidithioketopiperazine ring on a functionalized 7-hydroxytetrahydroindole ring while avoiding the potential aromatization reaction which the tetrahydroindole system presents. The starting point was methyl 1-benzyloxy-carbonyl-3a-hydroxy-6-oxo-2,3,3a,6,7,7a-hexahydroindol-2-carboxylate **1**, prepared by Wipf and Kim by oxidative cyclization of tyrosine.[8] This material has the correct configuration at C2 and C7a and conversion to gliotoxin functionality requires redox modification with introduction of an *S*-hydroxyl group (β) at C7. Our initial concept was to use the β-orientation of the 3a-hydroxyl to establish the stereochemistry at C7. Work by Adam has shown that hydroxyl groups have *syn*-directing effects in singlet oxygen cycloadditions[9] and thus the diene **3** became the initial target. It was successfully prepared from **1** by reduction of the C6 carbonyl with $NaBH_4$-$CeCl_3$, acetylation and $Pd(OAc)_2$ mediated elimination.[10] The diene **3** was subjected to photooxidation. The best results achieved on a 150 mg scale involved use of a 300W Tungsten projection lamp with tetraphenylporphine (TPP) as the sensitizer in CH_2Cl_2. The endoperoxide **4a** was reduced immediately by zinc in acetic acid to provide the triol **4b**. Use of $CHCl_3$ or methanol as solvent or use of Rose Bengal as the sensitizer gave poorer results. The triol was then converted to the boronate **5a**, which was protected at the C7 hydroxyl using TBDMSOTf.[11] Removal of the boronate group by H_2O_2 gave **5c** in overall 30% yield from **4a**. This material was converted to the thiocarbonate **5d** using thiocarbonyldimidazole (TCDI). Warming with 1,3-dimethyl-2-phenyl-1,3,2-diazaphospholidine[12] gave **6** in 47% yield (Scheme 1). This provides a fully protected version of the 7-hydroxy-2,3,7,7a-tetrahydroindole component of the gliotoxin structure (Scheme 1).

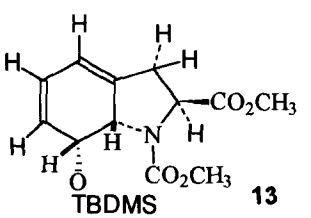
Scheme 1



a: $NaBH_4$, $CeCl_3$, MeOH (94%); b: Ac_2O, Et_3N, DMAP (90%); c: $Pd(OAc)_2$, Ph_3P, Et_3N, 110° (74%); d: O_2, hν, TPP, CH_2Cl_2 (87%); e: Zn, AcOH, THF, 0° (60%); $LiBHEt_3$, THF, then H_2O (not purified); g: TBDMSOTf, Et_3N (not purified); H_2O_2 (29% from **4b**); i: TCDI (71%); j: 1,3-dimethyl-2-phenyl-1,3,2-diazaphospholidine, 40° (47%).



C2	C3	C4	C5	C6	C7	C7a
4.37	2.41	5.31	5.58	5.67	4.67	4.84
$J_{2,3}$=8		$J_{4,5}$=5	$J_{5,6}$=10	$J_{6,7}$=<1	$J_{7,7a}$=12	
		$J_{4,7a}$=3	$J_{5,7}$=3			



C2	C3	C4	C5	C6	C7	C7a
4.44	2.74,2.95	5.87	6.12	5.95	4.58	4.27
$J_{2,3}$=7,8	$J_{3,3'}$=17	$J_{4,5}$=5	$J_{5,6}$=10	$J_{6,7}$=6	$J_{7,7a}$=<2	

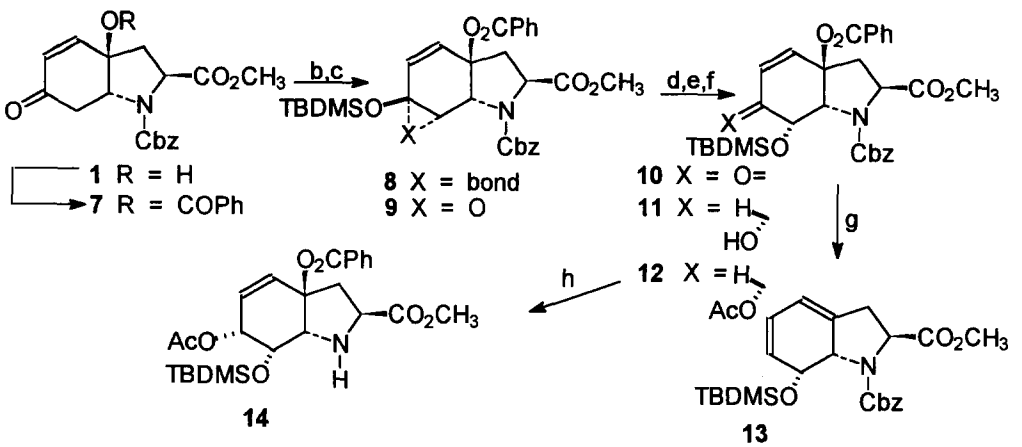
Figure 1. Chemical shift and coupling constants for compunds **6** and **13**.

As is true for most of the other Cbz-protected intermediates in this series, the NMR spectrum of **6** revealed signals due to two rotamers at ambient temperature. However coalescence could be observed >70° and detailed spectral analysis was carried out in toluene-d_8 at 100°. In addition to the readily assigned methyl, Cbz and TBDMS peaks, the spectrum contained seven series of peaks accounting for the eight ring protons. The C4, C5 and C6 vinyl protons were evident as an ABC system located at 5.31 (dd, J=5, 3 Hz) 5.58 (ddd, J=10, 5, 3 Hz) and 5.67 (d, J=10 Hz). The C7 and C7a protons appeared at 4.67 (dt) and 4.84 (dd), respectively. The C2 and C3 protons comprised a AMM' system at 4.37 and 2.41. Decoupling experiments were performed to confirm the assignments. The assignments and coupling constants are given in Figure 1.

The β (*S*) configuration was provisionally assigned to the C7 hydroxyl on the basis of the presumed directing effect of the C3a hydroxyl in the photoxidation.[9] The fact that the C3a and C4 hydroxyls readily form boronate and thiocarbonate rings in **5a** and **5d**, respectively, is consistent with this assignment. The coupling of 12 Hz observed between the C7 and C7a protons is also consistent with the *trans* diaxial arrangement in **6**.

While this route provided the 7-hydroxytetrahydroindole structure of gliotoxin with the correct stereochemistry, the overall yield was low (about 3.5% from **1**) and the scale of the photoxidation step was limited. A second route was therefore explored. The overall shape of **1** presents a convex and concave surface because of the *cis* ring fusion. A direct oxidation on a C6-C7 double bond from the convex face might then provide the desired *S*-stereochemistry at C7. While the 3a-benzoyloxy substituent is capable of shielding the β-face, the extent of shielding is dependent on the orientation of the benzoyl group with respect to the remainder of the ring. To explore this route, **1** was converted to the benzoate **7** which was then converted to the silyl enol ether **8**. Oxidation of **8** by dimethyldioxirane (DMDO) afforded **9**. Silyloxy epoxides are usually transient intermediates but they have been isolated occasionally.[13] The steric bulk of the TBDMS group also probably contributes to the relative stability of **9**. Heating **9** in 1,2-dichloroethane led to a clean rearrangement to a silyl-oxyenone **10**. This material was converted to a 7-*tert*-butyldimethylsilyloxy-2,3,7,7a-tetra-hydroindole in three steps. Compound **10** was reduced ($NaBH_4$, $CeCl_3$), acetylated (Ac_2O, DMAP, Et_3N) and then subjected to 1,4 reductive elimination using buffered sodium amalgam.[14] The product **13** was different from **6**, suggesting it must have 7-(*R*) (α) configuration. The efficiency of this synthesis is much higher (31% from **1** in seven steps) than the photoxidation route (Scheme 2).

Scheme 2



a: $(PhCO)_2O$, DMAP, Et_3N (80%); b: TBDMSOTf, Et_3N (84%); c: DMDO, 0°, (not purified); d: $ClCH_2CH_2Cl$, 83° (82%); e: $NaBH_4$, $CeCl_3$ (quant); f: Ac_2O, DMAP, Et_3N (96%); g: Na(Hg) MeOH, Na_2HPO_4 (58%); h: 10% Pd/C, cyclohexadiene.

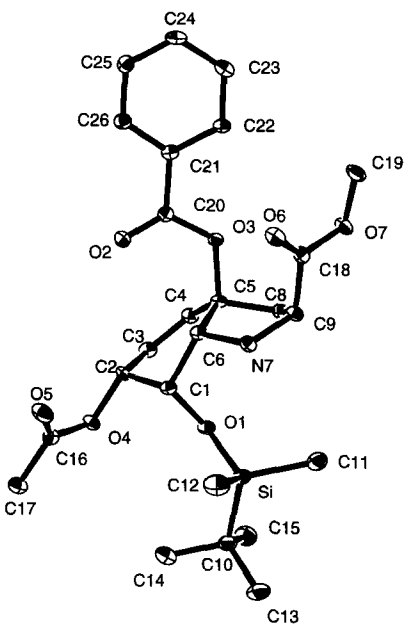


Figure 2. Ortep drawing of crystal structure of **14**.

Full coalescence of the rotamers in the ^{1}H NMR spectrum of **13** was achieved at 145° in DMSO. The spectrum was analyzed with decoupling, leading to the assignments in Figure 1. In particular, the H-7, H-7a coupling constant is <2 Hz, consistent with the 7-(*R*) stereochemistry. The structure and stereochemistry were further supported by an X-ray crystal structure on compound **14**, prepared by deprotection of intermediate **12**. This structure confirms the α-orientation of the C7 oxygen substituent (Figure 2). Since silyloxyepoxide rearrangements normally occur with retention of configuration,[15] the α-orientation of the 7-oxygen substituent implies that epoxidation took place from the concave α face, contrary to our initial expectation.

In order to explore the origin of the possible steric shielding by the benzoyloxy, benzyloxycarbonyl and *tert*-butyldimethylsilyloxy substituents, energy minimization was done for several conformations using the MM2 force field in the Cache system.[16] The benzoyloxy group was found to be oriented away from the C6-C7 double bond in all minima found and appeared unlikely to exert steric control. In the lowest minimum found, the TBDMS group was in a conformation in which the silyl substituent is oriented toward the α-face with one methyl group located beneath the C6-C7 double bond, suggestive of a β-orienting effect, which is opposite to the observed stereochemistry. However, a related conformation with the TBDMS group oriented toward the β face is within 1 kcal. The Monte Carlo conformation search routines of macro model program[17] also located as the global minimum conformation in which the TBDMS group is oriented toward the α face. These ground state structures do not offer a convincing explanation for the observed α stereoselectivity. DMDO is generally presumed to approach from the least hindered side of the molecule[18] but there have been few studies explicitly designed to explore this point.[19] Several specific instances exist where stereoselectivity appears to be under directive control of nearby substituents.[20]

These two routes provide stereochemically complementary routes to the 7-(*S*) and 7-(*R*) oxygenated tetrahydroindole rings found in gliotoxin. The results also demonstrate a considerable degree of stability for silylated hydroxycyclohexadiene intermediates such as **6** and **13**. It is particularly impressive that the 7-(*R*) isomer **13**, which has the potential for an aromatization by *trans*-elimination, survives several hours at 145° in DMSO during the decoupling NMR experiments. The stability of the protected 7-hydroxytetrahydroindole ring will be crucial to an overall synthetic strategy for gliotoxin involving such intermediates since it must survive introduction of the epidithioketopiperazine ring.

Experimental

General. All reactions except the photooxidation were run in an inert atmosphere (N_2 or Ar) in distilled solvents: MeOH, EtOH (from Mg/I_2); CH_2Cl_2, $CHCl_3$, $ClCH_2CH_2Cl$, CH_3CN, toluene, pyridine, Et_3N (from CaH); THF (from benzophenone, Na); acetone dried over 4A Molecular sieves). Chromatography was done with silica gel, 230-400 mesh. ^1H NMR spectra were recorded at 300 MHz and ^{13}C NMR at 75 MHz and chemical shifts are relative to TMS. Most of the carbobenzyloxy-protected compounds show ^1H spectra for two rotamers. The chemical shift of the peak of the major rotamer is listed first and coupling constants are given in Hz only for the major rotamer. In ^{13}C spectra, peaks listed together in parentheses are assigned to rotamers.

[2*S*-(2β,3aβ,6α,7aβ)]-2,3,3a,6,7,7a-Hexahydro-3a,6-dihydroxy-1*H*-indole-1,2-dicarboxylic acid 1-Benzyl 2-Methyl Ester **2a.** Hydroxyenone **1** (2.53 g, 7.3 mmol) was dissolved in MeOH (30 mL). $CeCl_3$ (1.8 g, 7.3 mmol) and $NaBH_4$ (280 mg, 7.4 mmol) were added and reaction was stirred for 10 min.[21] The reaction solution was diluted with water (30 mL) and extracted with EtOAc (1 x 50 mL, 2 x 30 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, and evaporated *in vacuo* to give 2.39 (94%) of **2a** as a cream-colored foam. This material was sufficiently pure for further use. ^1H NMR ($CDCl_3$) 7.37-7.27 (m, 5H); 5.81 (m, 1H); 5.68 (m, 1H); 5.22 + 5.19 (d, J=12, + d′, 1H); 5.12 + 5.00 (d, J=12, + d′, 1H); 4.51-4.37 (m, 2H); 4.15 + 4.09 (dd, J=10,5, + dd′, 1H); 3.55 + 3.80 (s + s′, 3H); 2.72 + 2.53 (m + m′, 1H); 2.45 (m, 1H); 2.17 +2.13 (d, J=8, + d′, 1H); 1.31 (m, 1H).

[2*S*-(2β,3aβ,6α,7aβ)]-2,3,3a,6,7,7a-Hexahydro-6-acetyloxy-3a-hydroxy-1*H*-indole-1,2-dicarboxylic acid 1-Benzyl 2-Methyl Ester **2b.** Allylic diol **2a** (2.17 g, 6.2 mmol) was dissolved in CH_2Cl_2 (30 mL) and cooled to 0°C. Et_3N (1.1 mL, 7.9 mmol), DMAP (38 mg, 0.31 mmol), and acetic anhydride (680 mL, 7.2 mmol) were added, and the solution was stirred for 1 h at 0°C. MeOH (0.5 mL) was added, and stirring was continued for 5 min. The solution was then washed with 1N HCl, sat. aq. $NaHCO_3$, and brine (20 mL each), dried over $MgSO_4$, and evaporated to yield 2.19 g (90%) of **2b** as an off-white foam. This material was sufficiently pure for further use. Four crystallizations from EtOAc/hexane provide an analytical sample as an off-white solid (mp 131-132°C). ^1H NMR ($CDCl_3$) 7.38-7.27 (m, 5H); 5.82-5.69 (m, 2H); 5.47 (m, 1H); 5.20 + 5.21 (d, J=13, + d′, 1H); 5.14 + 5.01 (d, J=13, + d′, 1H); 4.47 (t, J=10, 1H); 4.18 (m, 1H); 3.81 + 3.55 (s + s′, 3H); 2.75 + 2.58 (m + m′, 1H); 2.48 + 2.44 (dd, J=10,5, + dd′, 1H); 2.08 + 2.04 (d, J=8, + d′,

1H); 2.05 + 2.04 (s + s', 3H); 1.44 (m, 1H). MS (CI) m/z calcd. for $C_{20}H_{23}NO_7$ (389), found 390 (M+1). Anal. Calcd: C, 61.69; H, 5.95; N, 3.60. Found: C, 61.54; H, 5.98; N, 3.60.

[2*S*-(2β,3aβ,7aβ)]-2,3,3a,7a-Tetrahydro-3a-hydroxy-1*H*-indole-1,2-dicarboxylic acid 1-Benzyl 2-Methyl Ester **3.** Toluene (35 mL) which had been purged with argon for 30 min was added to allylic acetate **2b** (2.08 g, 5.3 mmol), $Pd(OAc)_2$ (24 mg, 0.11 mmol, 2 mol %), and Ph_3P (140 mg, 0.53 mmol, 10 mol %) to give a yellow solution. (10) Et_3N (0.9 mL, 6.5 mmol) was added, and then the solution was heated at reflux for 2h. The solution was cooled to room temperature, diluted with EtOAc (40 mL), and washed with 1N HCl, sat. aq. $NaHCO_3$, and brine (40 mL each). After drying over $MgSO_4$, evaporation gave an oil that was purified by chromatography on silica gel (5:2 hexane/EtOAc) giving 1.3 g (74%) of **3** as a yellow oil. ^1H NMR ($CDCl_3$) 7.38-7.28 (m, 5H); 6.06-5.80 (m, 4H); 5.28 + 5.25 (d, J=13, + d', 1H); 5.13 + 5.06 (d, J=13, + d', 1H); 4.79 + 4.85 (bs + bs', 1H); 4.27 (t, J=10, 1H); 4.17 + 3.81 (s + s', 1H); 3.83 + 3.57 (s + s', 3H); 2.31 + 2.36 (dd, J=10,4, + dd', 1H); 2.19 + 2.16 (m + m', 1H). MS (CI) m/z calcd. for $C_{18}H_{19}NO_5$ (329), found 330 (M+1).

[2*S*-(2β,3aβ,4β,7β,7aβ)]-2,3,3a,4,7,7a-Hexahydro-4,7-endoperoxy-3a-hydroxy-1*H*-indole-1,2-dicarboxylic acid 1-Benzyl 2-Methyl Ester **4a.** Diene **3** (416 mg, 1.26 mmol) and tetraphenylporphine (12 mg, 0.020 mmol) were dissolved in CH_2Cl_2 (60 mL). Oxygen was bubbled through the solution and the flask was irradiated with a 300W slide projector lamp for 9 h. The solvent was evaporated and the residue was taken up in MeOH (10 mL) and filtered through a small pad of Celite. The Celite pad was washed with MeOH (2 x 10 mL), and the filtrate was evaporated to give 396 mg (87%) of **4a** as a brown foam. This material was used without purification in the next reaction. ^1H NMR ($CDCl_3$) 7.38-7.27 (m, 5H); 6.64 (m, 1H); 6.54 + 6.38 (m + m', 1H); 5.53 (m, 1H); 5.19 + 5.25 (d, J=13, + d', 1H); 5.02 + 5.13 (d, J=13, + d', 1H); 4.55 (m, 1H); 4.32 + 4.36 (dd, J=9,2, + dd', 1H); 4.12 + 4.09 (d, J=5, + d', 1H); 3.61 + 3.76 (s + s', 3H); 2.57-2.09 (m, 2H).

[2*S*-(2β,3aβ,4β,7β,7aβ)]-2,3,3a,4,7,7a-Hexahydro-3a,4,7-trihydroxy-1*H*-indole-1,2-dicarboxylic acid 1-Benzyl 2-Methyl Ester **4b**. Crude endoperoxide **4a** (145 mg, 0.40 mmol) was dissolved in THF (2 mL) and AcOH (1 mL) and cooled to 0°C. Zinc dust (260 mg, 4.0 mmol) was added and the suspension was vigorously stirred for 1 h at 0°C. The excess zinc was removed by filtration and washed with EtOAc (3 x 5 mL).

The combined filtrate was washed with water (2 x 5 mL), and the combined aqueous layers were re-extracted with EtOAc (5 mL). The combined organic layers were washed with sat. $NaHCO_3$ (2 x 5 mL) and brine (5 mL), dried over $MgSO_4$, and evaporated to give a brown oil. Purification by chromatography on silica gel (1:3 hexane/EtOAc) yielded **4b** as a tan foam (88 mg, 57% overall from diene **4a**). Two recrystallizations of a sample from CH_2Cl_2/hexane provided colorless needles (mp 107-108°C). ^1H NMR ($CDCl_3$) 7.42-7.28 (m, 5H); 6.03 + 6.10 (ddd, J=10,5,2, + ddd', 1H); 5.89 + 5.93 (dd, J=10,3, + dd', 1H); 5.24 + 5.30 (d, J=13, + d', 1H); 5.10 + 5.14 (d, J=13, + d', 1H); 4.62 (bs, 1H); 4.42 (dd, J=7,5, 1H); 4.20-4.02 (m, 4H); 3.62 + 3.82 (s + s', 3H); 3.13 + 2.87 (bs + bs', 1H); 2.13 (m, 2H). ^{13}C NMR ($CDCl_3$) (173.7, 172.6); (156.4, 154.5); (135.3, 135.2); (130.8, 130.1); 128.6; 128.3; 128.2; 128.1; 127.8; 127.7; 127.5; (79.6, 77.9); (71.8, 70.9); (69.7, 69.1); 67.5; (66.8, 66.3); (57.6, 57.5); (52.5, 52.1); (39.3, 37.7). MS (CI) m/z calcd. for $C_{18}H_{21}NO_7$ (363), found 364 (M+1). Anal. Calcd.: C, 59.49; H, 5.83; N, 3.86. Found: C, 59.58; H, 5.84; N, 3.83.

[2*S*-(2β,3aβ,4β,7β,7aβ)]-2,3,3a,4,7,7a-Hexahydro-3a,4,7-trihydroxy-1*H*-indole-1,2-dicarboxylic acid 3a,4-(*B*-Ethylboronate) 1-Benzyl 2-Methyl Ester **5a**. Triol **4b** (400 mg, 1.1 mmol) was dissolved in THF (15 mL) and cooled to 0°C, and then $LiEt_3BH$ (1.0 M in THF, 2.3 mL, 2.3 mmol) was added dropwise. (11) The solution was stirred for 5 min at 0°C and then for 1 h at room temperature. Distilled water (420 mL, 23.3 mmol) was added and stirring was continued for 30 min. The solvent was evaporated and the residue was taken up in CH_2Cl_2 (15 mL) and filtered through a small pad of $MgSO_4$/Celite (5 g, 2:1 w/w). The pad was washed with additional CH_2Cl_2 (5 mL) and the filtrate was evaporated *in vacuo* to yield 464 mg (105%) of crude **5a** as a light yellow foam. ^1H NMR ($CDCl_3$) 7.40-7.31 (m, 5H); 5.87 (dt, J=10,2,2, 1H); 5.81 (dt, J=10,1,1, 1H); 5.74 (s, 1H); 5.28 (d, J=12, 1H); 5.12 (d, J=12, 1H); 4.57 (d, J=10, 1H); 4.53 (m, 1H); 4.08 (bd, 1H); 3.87 (d, J=7.5); 3.61 (s, 3H); 2.50 (d, J=13.5, 1H); 2.15 (dd, J=13.5,9, 1H); 0.89 (t, 3H); 0.77 (t, 2H). MS (CI) m/z calcd. for $C_{20}H_{24}BNO_7$ (401), found 402 (M + 1).

[2*S*-(2β,3aβ,4β,7β,7aβ)]-2,3,3a,4,7,7a-Hexahydro-7-(*tert*-butyldimethylsilyloxy)-3a,4-dihydroxy-1*H*-indole-1,2-dicarboxylic acid 3a,4-(*B*-Ethylboronate) 1-Benzyl 2-Methyl Ester **5b**. Crude hydroxy boronate **5a** (464 mg, 1.16 mmol) was dissolved in CH_2Cl_2 (10 mL) and cooled to 0°C. Et_3N (0.50 mL, 3.6 mmol) was added followed by TBSOTf (0.55 mL, 2.4 mmol). After 1 h at 0°C and 1 h at room temperature, TLC

(2:1 hexane/EtOAc) indicated that some starting material remained. More Et_3N (0.50 mL, 3.6 mmol) and TBSOTf (0.55 mL 2.4 mmol) were added. After 1 h, there was no starting material by TLC. The solution was washed with water (10 mL) and brine (10 mL), dried over $MgSO_4$, and evaporated to give 701 mg (>100%) of **5b** as an orange oil that was used without further purification. ^{1}H NMR ($CDCl_3$) 7.40-7.30 (m, 5H); 5.88-5.77 (m, 2H); 5.16 + 5.43 (d , J=12, + d', 1H); 5.02 + 4.96 (d, J=12, + d', 1H); 4.48 (m, 2H); 4.00 (m, 2H); 3.50 + 3.66 (s + s', 3H); 2.44-2.27 (m, 2H); 0.87 (m, 12H); 0.76 (t, 2H); 0.03 (m, 6H). MS (CI) m/z calcd. for $C_{26}H_{38}BNO_7Si$ (515), found 516 (M + 1).

[2*S*-(2β,3aβ,4β,7β,7aβ)]-2,3,3a,4,7,7a-Hexahydro-7-(*tert*-butyldimethylsilyloxy)-3a,4-dihydroxy-1*H*-indole-1,2-dicarboxylic acid 1-Benzyl 2-Methyl Ester **5c**. The crude TBDMS boronate **5b** from above was dissolved in EtOAc (10 mL). Distilled water (1.0 mL) and 30% H_2O_2 (1.0 mL) were added and the two-phase mixture was stirred vigorously for 1h.[17] The mixture was washed with water (2 x 10 mL) and brine (10 mL), dried over $MgSO_4$, and evaporated to give an orange oil. Purification by chromatography on silica (2:1 hexane/EtOAc) provided 150 mg (29% from **4b**) of **5c** as a colorless oil. ^{1}H NMR ($CDCl_3$) 7.38-7.28 (m, 5H); 6.40 + 6.36 (dd, J=10,5, + dd', 1H); 6.17 + 6.09 (dd, J=10,6, + dd', 1H); 5.29, 5.19, 5.05 (3 d's, 2H); 4.72 (m, 1H); 4.43 (m, 1H); 4.36 (dd, J=9,1); 4.12 (bs, 1H); 3.61 + 3.76 (s + s', 3H); 2.16 + 2.20 (d, J=15, + d', 1H); 2.06 + 2.03 (dd, J=15,1.5, + dd', 1H); 0.90 + 0.80 (s + s', 9H); 0.27 + (-0.04) (s + s', 3H); 0.17 + (-0.07) (s + s', 3H). ^{13}C NMR ($CDCl_3$) 172.3; 154.8; 153.6; (133.8, 132.3); (132.8, 132.3); 128.1; 128.0; 127.9; 127.9; 127.6; 127.5; (80.5, 80.4); (71.1, 69.9); (68.0, 67.8); (67.3, 66.8); (67.0, 65.2); (58.9, 58.6); (52.1, 51.9); (39.4, 38.4); (25.2, 25.1); -5.1; -5.3. MS (CI) m/z calcd. for $C_{24}H_{35}NO_7Si$ (477), found 478 (M + 1).

[2*S*-(2β,3aβ,4β,7β,7aβ)]-2,3,3a,4,7,7a-Hexahydro-7-(*tert*-butyldimethylsilyloxy)-3a,4-dihydroxy-1*H*-indole-1,2-dicarboxylic acid 3a,4-Thionocarbonate 1-Benzyl 2-Methyl Ester **5d**. Mono TBDMS ether **5c** (52 mg, 0.11 mmol) and TCDI (90%, 25 mg, 0.13 mmol) were dissolved in toluene (1 mL) and heated at reflux for 1 h. The solution was cooled to RT, diluted with EtOAc (5 mL), washed with water (2 x 5 mL) and brine (5 mL), dried ($MgSO_4$), and evaporated to give a yellow oil. Purification by chromatography on silica gel (3:1 hexane/EtOAc) gave **5d** as a colorless oil (40 mg, 71%). ^{1}H NMR ($CDCl_3$) 7.38-7.27 (m, 5H); 6.14 + 6.09 (bd, J=10, + bd', 1H); 5.94 + 5.91 (dd, J=10,3, + dd', 1H); 5.17 + 5.32 (d, J=12, + d', 1H);

5.01 (m, 2H); 4.43-4.20 (m, 3H); 3.50 + 3.72 (s + s', 3H); 2.65 (m, 1H); 2.53 + 2.49 (d, J=9, + d', 1H); 0.84 + 0.90 (s + s', 9H); 0.06 + 0.01 (s + s', 3H); 0.05 + (-0.01) (s + s', 3H). MS (CI) m/z calcd. for $C_{25}H_{33}NO_7SSi$ (519), found 520 (M+1).

[2*S*-(2β,7β,7aβ)]-2,3,7,7a-Tetrahydro-7-(*tert*-butyldimethylsilyloxy)-1*H*-indole-1,2-dicarboxylic acid 1-Benzyl 2-Methyl Ester **6**. TBDMS thionocarbonate **5d** (37 mg, 0.071 mmol) and 1,3-dimethyl-2-phenyl-1,3,2-diazaphospholidine (50 μL, 0.27 mmol) were diluted with THF (200 μL) and heated at 40°C in an oil bath[12] for 3 h. The solution was cooled to room temperature and then directly chromatographed on silica gel (8:1 hexane/EtOAc) to provide material (28 mg) which was contaminated with the phosphine sulfide. Chromatography of this material on silica (98:2 CH_2Cl_2/EtOAc) gave the pure diene **6** as a white solid (15 mg, 47%). ^{1}H NMR (toluene-d_8 at 100°C) 7.10-6.85 (m, 5H); 5.67 (d, J=10, 1H); 5.58 (ddd, J=10,5,3, 1H); 5.31 (dd, J=5,3, 1H); 5.08 (d, J=12, 1H); 4.97 (d, J=12, 1H); 4.84 (dd, J=12,3, 1H); 4.67 (ddd, J=12,2,2, 1H); 4.37 (t, J=8, 1H); 3.23 (s, 3H); 2.41 (d, J=8, 1H); 0.99 (s, 9H); 0.15 (s, 3H); 0.08 (s, 3H). ^{13}C NMR ($CDCl_3$) 134.6, 128.3, 127.8, 124.3, 117.9, 75.6, 67.0, 64.8, 62.4, 52.0, 34.5, 25.9, -4.7, -5.2. MS (CI) m/z calcd. for $C_{24}H_{33}NO_5Si$ (443); found 444 (M + 1), 443, 428, 400, 386, 268, 91.

[2*S*-(2β,3aβ,7aβ)]-2,3,3a,6,7,7a-Hexahydro-3a-benzoyloxy-6-oxo-1*H*-indole-1,2-dicarboxylic acid 1-Benzyl 2-Methyl Ester **7**. Hydroxyenone **1** (1.7 g, 4.9 mmol), benzoic anhydride (3.35 g, 14.8 mmol), Et_3N (2.1 mL, 15.1 mmol), and DMAP (60 mg, 0.49 mmol) were dissolved in $CHCl_3$ (40 mL) and heated at reflux for 48 h. The solution was washed with 1N HCl, sat. $NaHCO_3$, and brine (30 mL each), dried ($MgSO_4$), and evaporated. The crude material was purified by flash chromatography on silica gel (2:1→1:1 hexane/EtOAc) to yield **7** as an off-white foam (1.78 g, 80%). A small amount was recrystallized twice from EtOAc/hexane to give an analytical sample as a white solid mp 129-131°C. ^{1}H NMR ($CDCl_3$) 7.95-7.27 (m, 10H); 7.09 + 7.04 (d, J=10, + d', 1H); 6.14 + 6.12 (d, J=10, + d', 1H); 5.24 + 5.19 (d, J=12, + d', 1H); 5.11 + 5.05 (d, J=12, + d', 1H); 5.03 (m, 1H); 4.75 + 4.65 (dd, J=9,2, + dd', 1H); 3.59 + 3.33 (s + s', 3H); 3.47 + 3.27 (dd, J=16,7, + dd', 1H); 3.08 + 3.14 (bd, J=6, + bd', 1H); 2.73 + 2.62 (dd, J=15,9, + dd', 1H); 2.51 + 2.39 (dd, J=16,9, + dd', 1H). Anal. Calcd. for $C_{25}H_{23}NO_7$: C, 66.81; H, 5.16; N, 3.12. Found: C, 66.86; H, 5.20; N, 3.07.

[2*S*-(2β,3aβ,7aβ)]-2,3,3a,7a-Tetrahydro-3a-benzoyloxy-6-(*tert*-butyldimethylsilyloxy)-1*H*-indole-1,2-dicarboxylic acid 1-Benzyl 2-Methyl Ester **8**. Benzoate **7** (3.14 g, 7.0 mmol) and Et_3N (2.0 mL, 14.3 mmol) were dissolved in CH_2Cl_2 (45 mL) and TBSOTf (2.4 mL, 10.5 mmol) was added.[18] After 30 min , the solution was washed with cold sat. $NaHCO_3$ (45 mL), dried (Na_2SO_4), and evaporated to give a light yellow solid. This material was dissolved in a minimum of CH_2Cl_2 and passed through a small plug of silica (30 g) with 3:1 hexane/EtOAc (250 mL). Evaporation of the filtrate gave an off-white solid which was triturated with cold hexane (25 mL), filtered, washed with cold hexane (25 mL), and dried to give **8** as a white solid (3.3 g, 84%). Two recrystallizations from hexane gave an analytical sample mp 143-145°C. ^{1}H NMR ($CDCl_3$) 7.94-7.29 (m, 10H); 6.12 + 6.07 (d, J=10, + d′, 1H); 5.79 + 5.74 (dd, J=13,3, + dd′, 1H); 5.43 + 5.12 (t, J=2, + t′, 1H); 5.38 + 5.34 (m + m′, 1H); 5.37 + 5.23 (d, J=12, + d′, 1H); 5.08 + 5.03 (d, J=12, + d′, 1H); 4.43 + 4.50 (d, J=9, + d′, 1H); 3.62 + 3.35 (s + s′, 3H); 2.99 + 2.94 (bd, J=15, + bd′, 1H); 2.48 + 2.42 (dd, J=15,9, + dd′, 1H); 0.90 + 0.94 (s + s′, 9H); 0.07 + 0.21 (s + s′, 3H); 0.05 + 0.18 (s + s′, 3H). MS (CI) m/z calcd. for $C_{31}H_{37}NO_7Si$ (563), found 564 (M+1). Anal. Calcd.: C, 66.05; H, 6.62; N, 2.49. Found: C, 65.92; H, 6.69; N, 2.44.

[2*S*-(2β,3aβ,7α,7aβ)]-2,3,3a,6,7,7a-Hexahydro-3a-benzoyloxy-7-(*tert*-butyldimethylsilyloxy)-6-oxo-1*H*-indole-1,2-dicarboxylic acid 1-Benzyl 2-Methyl Ester **10**. TBDMS dienol ether **8** (300 mg, 0.53 mmol) was dissolved in acetone (6 mL) and cooled to 0°C. DMDO (0.13 M in acetone, 5.4 mL, 0.70 mmol) was added in one portion[13] and the solution was stirred for 30 min at 0°C. Evaporation of solvent gave the silyloxy epoxide **9** as a colorless oil. ^{1}H NMR ($CDCl_3$) 7.90-7.29 (m, 10H); 6.13 + 6.08 (d, J=10, + d′, 1H); 5.93 + 5.89 (d, J=10, + d′, 1H); 5.27 + 5.38 (d, J=12, + d′, 1H); 5.07 + 5.03 (d, J=12, + d′, 1H); 4.95 + 4.86 (d, J=3, + d′, 1H); 4.59 + 4.53 (d, J=9, + d′, 1H); 4.20 + 3.87 (d, J=3, + d′, 1H); 3.65 + 3.36 (s + s′, 3H); 2.77 + 2.83 (d, J=15, + d′, 1H); 2.29 + 2.27 (dd, J=15,10, + dd′, 1H); 0.88 + 0.93 (s + s′, 9H); 0.22 + 0.12 (s + s′, 3H); 0.18 + 0.07 (s + s′, 3H).

The crude epoxide was dissolved in 1,2-dichloroethane (5 mL) and heated at reflux for 2 h. The solvent was evaporated to give a light yellow oil. Purification by chromatography on silica gel (6:1 hexane/EtOAc) gave **10** as a white foam (255 mg, 82%). [A similar reaction on a 5 mmol scale provided a 73% yield of **10**.] A small amount was recrystallized twice from hexane to give an analytical sample as a white

solid, mp 101-103°C. ^{1}H NMR ($CDCl_3$) 8.00-7.28 (m, 10H); 7.02 + 6.96 (d, J=10, + d', 1H); 6.14 + 6.12 (dd, J=10,2 + dd', 1H); 5.22 + 5.25 (d, J=12, + d', 1H); 5.01 + 5.11 (d, J=12, + d', 1H); 5.03 + 4.99 (d, J=12, + d', 1H); 4.75-4.38 (m + dd, 2H); 3.60 + 3.34 (s + s', 3H); 2.95-2.85 (m, 2H); 0.82 + 0.80 (s + s', 9H); 0.02 + (-0.10) (s + s', 3H); 0.03 + (-0.12) (s + s', 3H). ^{13}C NMR ($CDCl_3$) (194.6, 194.4); (171.1, 170.6); (164.9, 164.7); (153.1, 153.0); (143.2, 142.6); (135.5, 135.3); 133.0; (129.3, 129.3); 129.3; 129.3; 129.1; 128.2; 128.2; 127.9; 127.7; 127.6; 127.2; (83.7, 82.8); (72.0, 70.5); (67.3, 66.9); (65.8, 65.1); (59.3, 59.0); (51.8, 51.7); (39.7, 39.0); 25.1; 17.4; -5.8; -5.9. MS (CI) m/z calcd. for $C_{31}H_{37}NO_8Si$ (579), found 580 (M+1). Anal. Calcd.: C, 64.22; H, 6.43; N, 2.42. Found: C, 64.33; H, 6.48; N, 2.37.

[2*S*-(2β,3aβ,6α,7α,7aβ)]-2,3,3a,6,7,7a-Hexahydro-3a-benzoyloxy-7-(*tert*-butyldimethylsilyloxy)-6-hydroxy-1*H*-indole-1,2-dicarboxylic acid 1-Benzyl 2-Methyl Ester **11**. Enone **10** (1.2 g, 2.1 mmol) was dissolved in THF (12 mL) and MeOH (12 mL) and placed in a room temperature water bath. $CeCl_3$ (510 mg, 2.1 mmol) was added followed by $NaBH_4$ (80 mg, 2.1 mmol).[21] After 5 min the reaction was neutralized with 1N HCl, diluted with water (40 mL), and extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (30 mL), dried ($MgSO_4$), and evaporated to give **11** as a white foam (1.2 g, 100%) which was used without further purification. ^{1}H NMR ($CDCl_3$) 7.92-7.27 (m, 10H); 5.93 + 5.85 (dd, J=10,3, + dd', 1H); 5.80 (m, 1H); 5.22 + 5.30 (d, J=12, + d', 1H); 5.00 + 5.08 (d, J=12, + d', 1H); 4.83 + 4.80 (d, J=3, + d', 1H); 4.72 + 4.44 (m + m', 1H); 4.57 (m, 2H); 3.28 + 3.55 (s + s', 3H); 2.82 + 2.73 (bd, J=13, + bd', 1H); 2.66 + 2.63 (dd, J=13,10, + dd', 1H); 1.92 + 1.88 (overlapping d, J=10, + d', 1H); 0.88 + 0.86 (s + s', 9H); 0.14 + (-0.06) (s + s', 3H); (-0.02) + (-0.14) (s + s', 3H). ^{13}C NMR ($CDCl_3$) (171.5, 170.9); (165.0, 164.6); 153.6; 135.6; 135.6; 133.6; (133.1, 132.6); 129.8; 129.1; 128.3; 128.1; 127.9; 127.8; 127.6; (123.8, 123.4); (85.6, 84.6); (72.2, 71.0); (68.7, 68.5); (67.1, 66.8); (64.3, 63.5); (58.9, 58.7); (51.7, 51.6); (40.0, 39.3); 25.5; 17.7; -5.0; -5.2; -5.5.

[2*S*-(2β,3aβ,6α,7α,7aβ)]-2,3,3a,6,7,7a-Hexahydro-6-acetyloxy-3a-benzoyloxy-7-(*tert*-butyl-dimethyl-silyloxy)-1*H*-indole-1,2-dicarboxylic acid 1-Benzyl 2-Methyl Ester **12**. Allylic alcohol **11** (1.2 g, 2.1 mmol) was dissolved in CH_2Cl_2 (20 mL). Et_3N (0.90 mL, 6.5 mmol), acetic anhydride (0.60 mL, 6.4 mmol), and DMAP (25 mg, 0.20 mmol) were added. After 4 h at room temperature, MeOH (0.5 mL) was added and stirring was continued for 10 min to consume excess Ac_2O. The solution was washed with 1N HCl, sat.

$NaHCO_3$, and brine (20 mL each), dried ($MgSO_4$), and evaporated to give **12** as a colorless foam (1.23 g, 96%) which was used without further purification. ^1H NMR ($CDCl_3$) 7.98-7.27 (m, 10H); 6.01 + 5.92 (dd, J=14,3, + dd', 1H); 5.70 (m, 2H); 5.21 + 5.33 (d, J=12, + d', 1H); 4.99 + 5.07 (d, J=12, + d', 1H); 4.85-4.54 (2m, 3H); 3.28 + 3.55 (s + s', 3H); 2.87-2.65 (m, 2H); 2.13 + 2.11 (s + s', 3H); 0.88 + 0.84 (s + s', 9H); 0.18 + (-0.15) (s + s', 3H); (-0.06) + (-0.21) (s + s', 3H). ^{13}C NMR ($CDCl_3$) (171.4, 170.8); (169.4, 169.3); (164.7, 164.4); 153.5; 135.6; 132.6; 129.7; 129.1; 128.2; 128.1; 127.9; 127.8; 127.6; (124.7, 124.4); (85.6, 84.5); (71.5, 71.2); (70.2, 69.0); (67.0, 66.7); (64.4, 63.5); (58.9, 58.7); (51.7, 51.6; (39.8, 39.2); 25.3, (20.7, 20.7); 17.7; (-5.1, -5.2); (-5.5, -6.0).

[2*S*-(2β,7α,7aβ)]-2,3,7,7a-Tetrahydro-7-(*tert*-butyldimethylsilyloxy)-1*H*-indole-1,2-dicarboxylic acid 1-Benzyl 2-Methyl Ester **13**. Allylic acetate **12** (100 mg, 0.16 mmol) was dissolved in THF (4.5 mL) and MeOH (1.5 mL). Na_2HPO_4 (160 mg, 1.1 mmol) was added and the mixture was cooled to -20°C. Na(Hg) (5%, 740 mg, 1.6 mmol Na) was added and the mixture was stirred at -20°C for 30 min.[14] The reaction mixture was filtered through a small plug of silica (1 g) and the silica was washed with EtOAc (20 mL). Evaporation of the filtrate gave a crude product which was purified by chromatography on silica gel (8:1 hexane/EtOAc) to give **13** as a colorless oil (41 mg, 58%). ^1H NMR ($CDCl_3$) 7.38-7.30 (m, 5H); 6.05 (m, 1H); 5.94-5.78 (m, 2H); 5.23 + 5.29 (d, J=12. + d', 1H); 4.94 + 5.06 (d, J=12, + d', 1H); 4.71-4.38 (m, 3H); 3.43 + 3.77 (s + s', 3H); 2.90 (m, 1H); 2.76 (m, 1H); 0.78 + 0.79 (s + s', 9H); (-0.01) + (-0.10) (s + s', 3H); (-0.01) + (-0.12) (s + s', 3H). ^1H NMR (DMSO-d_6 at 145°C) 7.40-7.30 (m, 5H); 6.12 (dd,J=10,5, 1H); 5.95 (dd, J=10,6, 1H); 5.87 (m, 1H); 5.17 (bs, 2H); 4.58 (m, 1H); 4.44 (dd, J=8,7, 1H); 4.27 (m, 1H); 3.57 (s, 3H); 2.95 (dd, J=17,8, 1H); 2.74 (dd, J=17,7,); 0.79 (s, 9H); -0.03 (s, 3H); -0.05 (s, 3H). ^{13}C NMR ($CDCl_3$) (172.6, 172.4); (154.5, 153.6); 137.6; 136.5; 135.7; 128.1; 127.9; 127.8; 127.7; 127.6; (126.2, 125.9); (125.2, 125.0); (115.5, 115.4); (67.0, 66.7); (63.0, 62.4); (62.1, 61.0); (61.2, 60.6); (51.9, 51.5); (33.9, 33.5); 25.2; 17.4; (-4.4, -4.5); (-5.4, -5.5). MS (CI) m/z calcd. for $C_{24}H_{33}NO_5Si$ (443); found 444 (M + 1), 443, 442, 428, 400, 386, 268, 91.

[2*S*-(2β,3aβ,6α,7α,7aβ)]-2,3,3a,6,7,7a-Hexahydro-6-acetyloxy-3a-benzoyloxy-7-(*tert*-butyl-dimethylsilyloxy)-1*H*-indole-2-carboxylic acid Methyl Ester **14**. Allylic acetate **12**(100 mg, 0.16 mmol) was dissolved in EtOH (1.5 mL). 10 % Pd/C (100 mg) was added followed by 1,4-cyclohexadiene (150 mL, 1.6

mmol).[24] The mixture was vigorously stirred for 4 h at room temperature. The catalyst was filtered off through a pad of Celite and the pad was washed with EtOAc (15 mL). Evaporation of the filtrate provided an off-white solid which was chromatographed on silica (7:1 hexane/EtOAc) to provide **14** as a colorless solid. A small amount was recrystallized from hexane (mp 128-131°C; softens around 113°C). Crystals suitable for X-ray analysis were obtained by allowing a hot hexane solution to cool slowly while surrounded by an initially warm (40°C) water bath. ^{1}H NMR ($CDCl_3$) 7.88 (m, 2H); 7.53 (m, 1H); 7.42 (m, 2H); 6.19 (dd, J=10,3, 1H); 5.75 (bd, J=10, 1H); 5.57 (app q, J=3, 1H); 4.23 (bs, 1H); 4.10 (d, J=3, 1H); 3.96 (dd, J=9,3, 1H); 3.57 (s, 3H); 2.86 (dd, J=14,3, 1H); 2.56 (dd, J=14,9, 1H); 0.91 (s, 9H); 0.14 (s, 3H); 0.09 (s, 3H). ^{13}C NMR ($CDCl_3$) 175.2, 170.1, 165.2, 132.8, 130.5, 129.4, 128.9, 128.2, 127.0, 86.8, 72.9. 71.3, 63.8, 59.3, 52.0, 41.1, 25.8, 21.2, 18.2 -4.4, -5.2. MS (CI) m/z calcd. for $C_{25}H_{35}NO_7Si$ (489), found 490 (M + 1). Anal. Calcd.: C, 61.32; H, 7.21; N, 2.86. Found: C, 61.41; H, 7.23; N, 2.85.

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